



Under What Circumstances Could Pediatric Extrapolation Occur?

Chairs:

Manpreet Singh, MD, MS

Robert Nelson, MD, PhD



Speakers

Dana Cahill, PhD

Tiffany Farchione, MD

Shamir Kalaria, PharmD, PhD

Forrest Williamson, PhD

Lynne Yao, MD

Manpreet Singh, MD, MS

Robert Nelson, MD, PhD

Disclosure of Potential Conflicts (Singh, Past 3 Years)

Source	Advisory Board/ Consultant	Research Support	Royalties	Honorarium
National Institutes of Health (NIMH, NIA)		X		
Brain and Behavior Research Foundation (BBRF)		X		
Patient-Centered Outcomes Research Institute		X		
Stanford Dept of Psychiatry and Behavioral Sciences		X		
Johnson & Johnson Services, Inc.		X		
Sunovion Pharmaceuticals	X			
Skyland Trail	X			
Johnson & Johnson Services, Inc.	X			
Alkermes	X			
AbbVie	X			
Boehringer-Ingelheim	X			
Karuna Therapeutics, Inc.	X			
Neumora	X			
American Psychiatric Association Publishing			X	
Thrive Global			X	
American Academy of Child and Adolescent Psychiatry				X
Past: Limbix Health and X, Moonshot Factory, Alphabet, Inc.	X			

SCHEDULE

2:00-2:05pm	Intro	Manpreet Singh, MD MS Robert Nelson, MD PhD
2:05-2:25pm	Pediatric Extrapolation Guidance Framework	Lynne Yao, MD
2:25-2:35pm	Discussion	Robert Nelson, MD PhD
2:35-2:55pm	Optimizing Pediatric Drug Development in Psychiatry: Quantitative Methods to Support Extrapolation of Efficacy	Shamir Kalaria, PharmD, PhD
2:55-3:05pm	Discussion	Manpreet Singh, MD MS
3:05-3:25pm	Innovative pediatric trials: A statistical examination of design and analysis strategies	Forrest Williamson, PhD
3:25-3:35	Discussion	Robert Nelson, MD PhD
3:35-3:50	Break	
3:50-4:20pm	Pathways for Extrapolation in Psychiatry	Tiffany Farchione, MD
4:20-4:30pm	Discussion	Manpreet Singh, MD MS
4:30-4:40pm	A recent example of pediatric extrapolation in psychiatry	Dana Cahill
4:40-5:30pm	Panel discussion	

Contemporary Drug Development Challenges in Child Psychiatry (that extend to CNS)

CHALLENGES

- Progress in novel therapeutics has been slow.
- Drug trials include participants from a wide age and symptom range.
- A strong placebo response has been observed, especially in pediatric MDD trials.
- Subjective/divergent symptom reports (parents/children) may affect signal detection.
- Implementation of evidence-based treatments remains difficult.
- Off-label prescribing is common; so are gaps in evidence.

OPPORTUNITIES

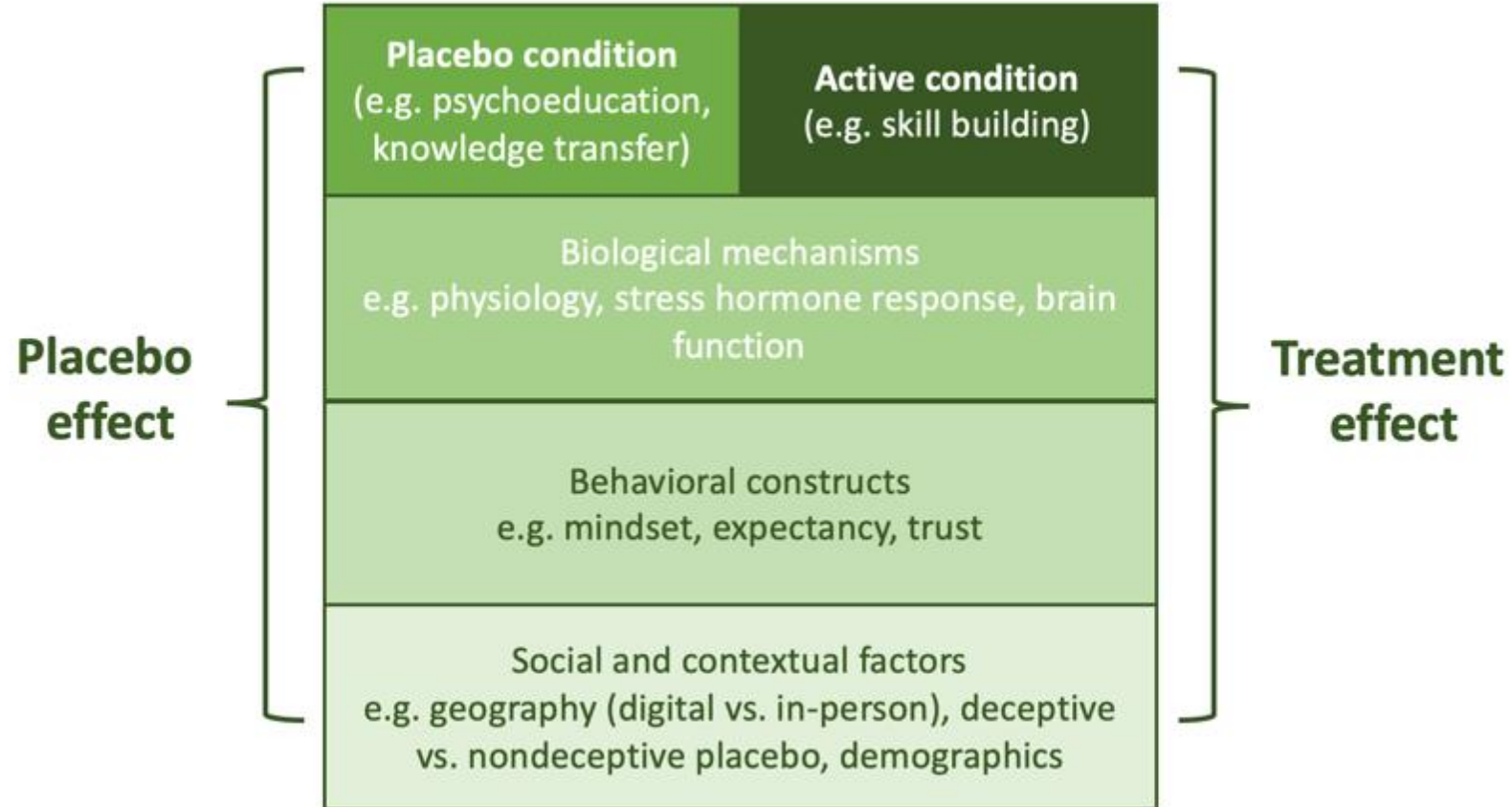
- Pediatric extrapolation
- Understand safety and bioavailability considerations
- Investigate complementary treatments (rational combination strategies) and comparative effectiveness (personalized treatments)
- Investigate the placebo response
- Patient centricity: Consider functional and quality of life outcomes
- Investigate interventions that improve adherence
- Conduct research in diverse populations

Why are placebo responses so common in pediatric depression trials? What factors predict response to treatment versus response to placebo?

Historical context:

- Pooled standard mean difference between treatment and placebo lower in pediatric versus adult depression trials
- Moderators of placebo response:
 - number of trial sites (US vs Global)
 - self-reported > clinician reported outcomes
 - lower baseline depression severity
- What will it be like moving forward?

A developing framework:



Hetrick et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database Syst Rev.* 2021 May 24;5(5):CD013674|; Feeney et al., Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis. *J Affect Disord.* 2022 May 15;305:55-64; Meister et al., Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. *Eur Child Adolesc Psychiatry.* 2020 Mar;29(3):253-273. de Villiers et al., Vantage Sensitivity: a framework for individual differences in response to psychological intervention, *SPPE*, 2018; [Mindsets Matter: A New Framework for Harnessing the Placebo Effect in Modern Medicine](#). Zion SR, Crum AJ. *Int Rev Neurobiol.* 2018;138:137-160; Singh et al., Can Translational Social Neuroscience Research Offer Insights to Mitigate Structural Racism in America? *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, April, 2022.